REMARKS

Claims 1-51 are pending. Claims 23, 24, 26-29, 32-40 and 44-51 were withdrawn from consideration. Claims 3 and 4 were objected to. Claims 1-22, 25, 30, 31 and 41-43 are rejected.

Applicant wishes to thank the Examiner for the helpful suggestions provided during the recent telephone conference with the undersigned. The Examiner's comments have been incorporated into the present "Amendment and Response".

The Specification has been amended to correct obvious typographical errors in paragraphs [00055] and [00157]. The term "EC_{50}" was corrected to read "IC_{50}". Support for this amendment can be found, for example, in paragraph [00157] which lists values for CC_{50}, IC_{50}, IC_{90} and SI, but does not refer to EC_{50}. The IC_{50} data for ADI-PEG20 was also corrected to properly indicate the position for the decimal point. One of skill in the art would readily determine that the decimal point listed in the specification as filed was in error. First, the skilled artisan would realize that the IC_{50} value should be less than the IC_{90} value. The skilled artisan would also understand that by manipulating the components for the SI value for ADI-PEG20, one would arrive at the proper IC_{50} value, 0.027 IU/ml. If the originally filed IC_{50} value was used in the calculation of the SI for ADI-PEG20, a value of 1.2 would result which specifically contradicts statements in the application that ADI-PEG20 is selective, including, for example, in the last sentence of paragraph [00157].

Claims 1, 3, 4, 6, 25 and 42 have been amended. Claims 1, 25 and 42 were amended to recite that the method relates to inhibition of HCV replication. As amended, claim 1 has the scope of claim 21 as originally filed, claim 25 has the scope of an embodiment of claim 31 as filed, and claim 42 has the scope of claim 43 as originally filed. Applicant notes that the claims, including, for example, claims 21, 31 and 43, were found free of the art. Applicant may pursue claims directed to inhibition of other viruses in related applications.

Claim 3 was amended to rectify the issue identified by the Office relating to antecedent support.

Claim 4 was amended to correct a typographical error by adding a "." at the end of the claim.

Claim 6 was amended to further clarify the claim.

Claims 20, 21, 30, 31 and 43 were cancelled without prejudice as duplicative of amended claims 1, 25 and 42.

Withdrawn claims 23, 24, 26-29, 32-40 and 44-51 have been cancelled without prejudice.

New claim 52 was added, support for which can be found, for example, in paragraphs [00109] and [00117].

New claim 53 was added, support for which can be found, for example, in Examples 7, 8 and 9. Example 9, for example, demonstrates the reduction in HCV titer in subjects of a human clinical trial.

New claims 54-71 were added and correspond to claims as originally filed dependent on claim 1.

New claims 72 and 73 were added, support for which can be found, for example, in paragraph [00094].

No new matter has been added to the application via the amendments discussed above.

Objections

The Office objected to claims 3 and 4. With respect to claim 3, the Office alleged that there was insufficient antecedent basis for the term "other antiviral compounds". Applicant amended claim 3 to replace "other antiviral compounds" with the phrase "conventional antiviral compounds", thereby rendering the objection moot. Support for this amendment can be found throughout the application as originally filed including, for example, in paragraph [00109].

With respect to claim 4, the Office notes that a "." is missing at the end of the claim. Applicant has amended claim 4 to supply the omitted "." .

Applicant respectfully requests the withdrawal of the claim objections.

Rejection under 35 U.S.C. §112, second paragraph

Claim 6 was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. The Office alleges that the terms "less than about", "at least 50% in greater than 50% of cells" are unclear. Although Applicant respectfully asserts that the art skilled would readily understand the metes and bounds of claim 6, Applicant has amended claim 6 to recite "The method of claim 1 wherein said composition comprising an arginine deiminase bonded to polyethylene glycol is effective at a concentration of less than 1 mM to inhibit viral replication by at least 50%." Applicant asserts that the metes and bounds of claim 6, as amended, would be readily understood by one of ordinary skill in the art.

Applicant respectfully requests withdrawal of the rejection of claim 6 under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1-22, 25, 30, 31 and 41-43 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. It is asserted that the claims are directed to "a large genus of genotypically and phenotypically disparate viruses"; that "the role of nitric acid in viral replication is not definitive", that "in vitro data does not correlate with in vivo data and/or clinical observation", and that the "working examples do not provide any evidence that ADI-PEG is effective as an antiviral agent."

Applicant respectfully disagrees and notes that it is well established that the description is presumed to be enabled and that in order to sustain an enablement rejection under the first paragraph of 35 U.S.C. §112, the Examiner must establish, using reasoning and evidence, that those skilled in the art would doubt the objective truth of Applicant's assertion that the claimed invention is enabled. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971); MPEP § 2163.

In the present application the Examiner has failed to meet this burden. When all the evidence is viewed in its totality, one skilled in the art would accept the objective truth of Applicant's assertion of enablement. No evidence has been provided to support some of the positions asserted in the Office Action and it appears that the Office has

apparently overlooked at least one specific example in the application addressing many of the issues raised in the Office Action. The enablement rejection set forth in the Office Action does not support or establish the conclusion that one skilled in the art would conclude that it would require undue experimentation to practice the claimed invention. When viewed in the aggregate, the evidence supports Applicant's assertions that the claims are enabled.

Inhibition of HCV replication with ADI-PEG is discussed in detail in the specification including, for example, in Examples 7, 8 and 9. Examples 7 and 8 provide *in vitro* data demonstrating the effect of ADI-PEG on selectively reducing HCV replication and HCV titer without causing cell death. Example 9 sets forth the results of human clinical trials which further demonstrate the effect of ADI-PEG on selectively reducing HCV titer.

1. The claims are not directed to a large genus of genotypically and phenotypically disparate viruses

The Examiner alleges that the specification "fails to teach how to make and use the full scope of the claimed invention without undue experimentation" and notes that a large number of "genotypically and phenotypically disparate viruses" are encompassed by the pending claims.

Applicant notes that as discussed above, the claims have been amended to refer to inhibition of HCV replication. Accordingly, the pending claims are not directed to "a large genus of genotypically and phenotypically disparate viruses."

The Office also alleges that "the inhibitory activity of an antiviral agent against a particular virus cannot be equated with its inhibitory effect against another virus." (citing Wiltink et al. and Saunders et al.). Although Applicant disagrees and notes that neither Wiltink nor Saunders represents the view of the art-skilled at the time the present application was filed (Wiltink was published in 1991 and Saunders was published in 1992), Applicant notes that the Examiner's point is moot in view of the amendment of claims 1 and 42 to recite inhibition of HCV replication.

2. The role of nitric acid in HCV replication is not part of the claims but the data indicate that it is definitive

The Office further suggests that the mechanism of action speculated on in the specification—the "lowering [of] extracellular arginine which inhibits nitric oxide synthesis" – is not definitive. The Office refers to references which are said to disclose that the role of NO is "unequivocal in inhibiting or increasing viral replication" in HIV, stating that the role of NO "is sometimes helpful and other times damaging to the host." (citing Torre et al.).

Applicant first notes that the pending claims neither recite nor require a particular mechanism of action. Notwithstanding the foregoing, Applicant asserts that at least one mechanism of action disclosed in the application (the lowering of NO) is supported by at least Example 9. For example, paragraph [00167] specifically recites that treatment of HCV "with ADI-SS PEG 20,000 mw results in a dose dependent decrease in plasma arginine and concomitant decrease in NO synthesis (data not shown)" and that the decrease was significant.

Applicant also notes that the pending claims are not directed at HIV, the subject of the Torre et al. reference.

3. The working examples provide evidence that ADI-PEG is effective as an antiviral agent

The Examiner alleges that the "working examples do not provide any evidence that ADI-PEG is effective as an antiviral agent". The Office states that working Examples 7 and 8 are directed to an *in vitro* experiment using the hepatoblastome cell and that:

> it is well known that ADI kills hepatoblastome cells in vitro and in vivo. Thus, in the working examples, the cells are killed by ADI-PEG, and in the absence of viable cells, viral replication in limited. ... The working examples fail to demonstrate that ADI-PEG inhibits viral replication."

Preliminarily, Applicant notes that it appears that the Office has overlooked evidence present throughout the application as filed that ADI-PEG is an effective anti-HCV agent. Applicant notes that *in vitro* evidence that ADI-PEG is an effective anti-

HCV agent is set forth in Examples 7 and 8, and that results of the use of ADI-PEG as an anti-HCV agent in a human clinical trial are set forth in Example 9.

Example 7 demonstrates that ADI-PEG selectively inhibits HCV replication but does not kill the cells. Example 7 includes as a control a measurement of the effect of ADI-PEG on the house-keeping gene actin in a stably HCV RNA replicating cell line AVA5 derived by transfection of a human hepatoblastome cell line Huh7. As set forth in paragraph [00155], ADI-PEG, while causing an 86% inhibition of HCV mRNA, yielded only a 12% inhibition of actin mRNA. This study confirms that the cells were not killed by the ADI-PEG.

Example 8 also demonstrates that ADI-PEG is a selective inhibitor of HCV replication. The selective index (SI) determined for ADI-PEG20 was determined to be 12. As set forth in paragraph [00157], an "SI >10 is considered to be a selective inhibition of the viral replication" and the "data confirm that ADI-PEG20 inhibits HCV replication and that this drug is selective".

Example 9 reports that treatment of humans chronically infected with HCV with ADI-PEG "results in significantly lower titers of HCV in their plasma". In a first study of 5 human patients, HCV titer in patients dropped an average of 65.8%. (See paragraph [00159]). In a second study of 15 patients, nine patients exhibited an average drop in HCV titer of about 74% post treatment (see paragraph [00169]).

Accordingly, one of skill in the art armed with the present application would agree that ample evidence was set forth that ADI-PEG is effective as an antiviral agent and that ADI-PEG inhibits HCV replication without killing host cells. The Examiner has proffered no evidence to support any contrary conclusion.

4. *In vitro* data does correlate with *in vivo* data and/or clinical observation

As discussed above, the *in vitro* data does set forth in the specification does correlate with *in vivo* data. Preliminarily, Applicant points out that the Office has provided no reasoning to support the allegation that the *in vitro* results do not correlate with the *in vivo* results. Nevertheless, the data in the working examples describing a human clinical trial (Example 9) confirms that the findings of Examples 7 and 8 that

ADI-PEG decreases HCV replication are predictive. The *in vitro* data demonstrates that HCV replication is inhibited without killing host cells. The human *in vivo* data demonstrates that HCV viral titer is decreased following treatment with ADI-PEG.

Accordingly, one of skill in the art armed with the present application would agree that the *in vitro* data correlates with the *in vivo* data.

The invention is enabled

One skilled in the art, armed with Applicant's disclosure and ordinary skill, could readily make and use the claimed invention without undue experimentation. When all of the *Wands* factors are considered together and the assertions made by the Office are viewed in the aggregate, it is clear that the specification fully supports a finding that the claimed invention is enabled. One skilled in the art would not conclude that undue experimentation would be necessary to practice the claimed invention. The specification provides adequate support to allow one having ordinary skill in the art to practice the claimed invention without undue experimentation. Indeed, in view of the presence of a detailed working example of a human clinical trial, Applicant asserts that no further experimentation would be required to practice the claimed invention. Indeed, the Office has failed to even recite what additional experimentation might be necessary to practice the claimed invention. One skilled in the art would also conclude that the specification fully supports the breadth of the claims. Again, as a working clinical trial is set forth in the specification, Applicant asserts that the requirement for a reasonable expectation of success has also been met.

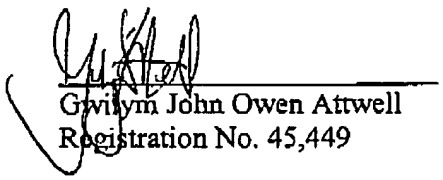
When all the evidence is viewed in its totality, one skilled in the art would accept the objective truth of Applicant's assertion of enablement. There is no evidence that would raise any doubts as to the enablement of the present invention, particularly in view of the Examples set forth. Accordingly, the Examiner must accept the objective truth of Applicant's assertion.

The claimed invention is enabled. Accordingly, Applicant respectfully requests the reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Docket No.: PHOE0001-100 **PATENT**
Filing Date: September 29, 2003 **Serial No.: 10/674,666**

The examination of these claims and passage to allowance are respectfully requested. An early Notice of Allowance is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 665-6904 to clarify any unresolved issues raised by this response.

Respectfully submitted,



Gwilym John Owen Attwell
Registration No. 45,449

Date: February 11, 2005
COZEN O'CONNOR, P.C.
1900 Market Street
Philadelphia, PA 19103-3508
Telephone: (215) 665-2000
Facsimile: (215) 701-2004

PHILA1\2213064\2 140707.000